1. NAME OF THE MEDICINAL PRODUCT

Dexilant delayed-release Capsules 30mg
Dexilant delayed-release Capsules 60mg

2. NAME AND STRENGTH OF ACTIVE SUBSTANCES

Dexilant is available in two dosage strengths: 30 mg and 60 mg, per capsule. Each capsule contains enteric-coated granules consisting of dexlansoprazole (active ingredient) and the following excipients:
Excipients: Sugar spheres, magnesium carbonate, sucrose, low-substituted hydroxypropyl cellulose, titanium dioxide, hydroxypropyl cellulose, hypromellose 2910, talc, methacrylic acid copolymers, polyethylene glycol 8000, triethyl citrate, polysorbate 80, colloidal silicon dioxide, hypromellose, carrageenan, potassium chloride,
FD&C Blue No. 2 aluminum lake (Blue capsule) and black ferric oxide (Gray capsule).

3. PRODUCT DESCRIPTION

30 mg delayed-release capsules are opaque, blue and gray with TAP and “30” imprinted on the capsule.
60 mg delayed-release capsules are opaque, blue with TAP and “60” imprinted on the capsule.

4. CLINICAL PHARMACOLOGY

ATC code: A02BC06

4.1 Mechanism of Action

Dexlansoprazole is a PPI that suppresses gastric acid secretion by specific inhibition of the (H^+,K^+)-ATPase in the gastric parietal cell. By acting specifically on the proton pump, dexlansoprazole blocks the final step of acid production.

4.2 Pharmacodynamics

Antisecretory Activity

The effects of Dexilant 60 mg (n=20) or lansoprazole 30 mg (n=23) once daily for five days on 24-hour intragastric pH were assessed in healthy subjects in a multiple-dose crossover study. The results are summarized in Table 1.

Table 1: Effect on 24-hour Intragastric pH on Day 5 After Administration of Dexilant or Lansoprazole in Adults

Dexilant 60 mg	**Lansoprazole 30 mg**
Mean Intragastric pH	
4.55	4.13
% Time Intragastric pH > 4 (hours)	
71 (17 hours)	60 (14 hours)

Serum Gastrin Effects

The effect of Dexilant on serum gastrin concentrations was evaluated in approximately 3460 patients in clinical trials up to 8 weeks and in 1023 patients for up to 6 to 12 months. The mean fasting gastrin concentrations increased from baseline during treatment with Dexilant 30 mg and 60 mg doses. In patients treated for more than 6 months, mean serum gastrin levels increased during approximately the first 3 months of treatment and were stable for the remainder of treatment. Mean serum gastrin levels returned to pre-treatment levels within one month of discontinuation of treatment.
During treatment with antisecretory medicinal products, serum gastrin increases in response to the decreased acid secretion. Also CgA increases due to decreased gastric acidity. The increased CgA level may interfere with investigations for neuroendocrine tumours.

Available published evidence suggests that proton pump inhibitors should be discontinued between 5 days and 2 weeks prior to CgA measurements. This is to allow CgA levels that might be spuriously elevated following PPI treatment to return to reference range.

Enterochromaffin-Like Cell (ECL) Effects

There were no reports of ECL cell hyperplasia in gastric biopsy specimens obtained from 653 patients treated with Dexilant 30 mg, 60 mg or 90 mg for up to 12 months.

During lifetime exposure of rats dosed daily with up to 150 mg per kg per day of lansoprazole, marked hypergastrinemia was observed followed by ECL cell proliferation and formation of carcinoid tumors, especially in female rats.

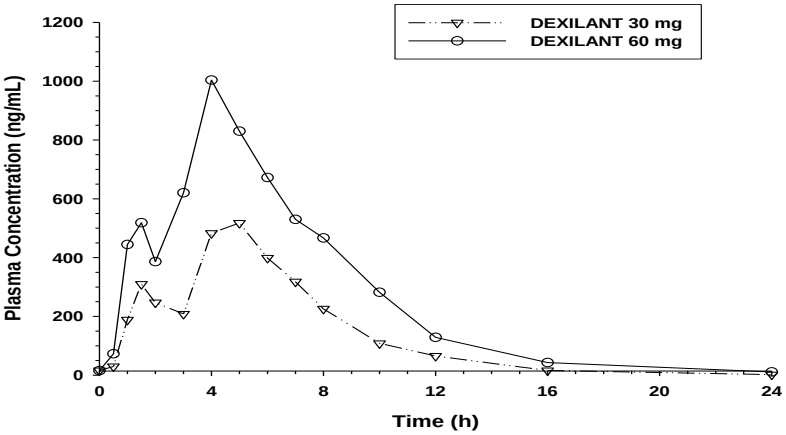
Effect on Cardiac Repolarization

A study was conducted to assess the potential of Dexilant to prolong the QT/QT_c interval in healthy adult subjects. Dexilant doses of 90 mg or 300 mg did not delay cardiac repolarization compared to placebo. The positive control (moxifloxacin) produced statistically significantly greater mean maximum and time-averaged QT/QT_c intervals compared to placebo.

4.3 Pharmacokinetic properties

The dual delayed release formulation of Dexilant results in a dexlansoprazole plasma concentration-time profile with two distinct peaks; the first peak occurs 1 to 2 hours after administration, followed by a second peak within 4 to 5 hours (see Figure 1). Dexlansoprazole is eliminated with a half-life of approximately 1 to 2 hours in healthy subjects and in patients with symptomatic GERD. No accumulation of dexlansoprazole occurs after multiple, once daily doses of Dexilant 30 mg or 60 mg, although mean AUC_t and C_{max} values of dexlansoprazole were slightly higher (less than 10%) on day 5 than on day 1.

Figure 1: Mean Plasma Dexlansoprazole Concentration – Time Profile Following Oral Administration of 30 or 60 mg DEXILANT Capsules Once Daily for 5 Days in Healthy Adult Subjects



The pharmacokinetics of dexlansoprazole are highly variable, with percent coefficient of variation (CV%) values for C_{max}, AUC, and CL/F of greater than 30% (see Table 2.)

Table 2: Mean (CV%) Pharmacokinetic Parameters for Adults Subjects on Day 5 After Administration of Dexilant

Dose (mg)	C_{max} (ng/ml)	AUC24 (ng·h/mL)	CL/F (L/h)
30	658 (40%) (N=44)	3275 (47%) (N=43)	11.4 (48%) (N=43)
60	1397 (51%) (N=79)	6529 (60%) (N=73)	11.6 (46%) (N=41)

Absorption

After oral administration of Dexilant 30 mg or 60 mg to healthy subjects and symptomatic GERD patients, mean C_{max} and AUC values of dexlansoprazole increased approximately dose proportionally (see Figure 1).

Distribution

Plasma protein binding of dexlansoprazole ranged from 96.1% to 98.8% in healthy subjects and was independent of concentration from 0.01 to 20 mcg per mL. The apparent volume of distribution (V_z/F) after multiple doses in symptomatic GERD patients was 40.3 L.

Metabolism

Dexlansoprazole is extensively metabolized in the liver by oxidation, reduction, and subsequent formation of sulfate, glucuronide and glutathione conjugates to inactive metabolites. Oxidative metabolites are formed by the cytochrome P450 (CYP) enzyme system including hydroxylation mainly by CYP2C19, and oxidation to the sulfone by CYP3A4.

CYP2C19 is a polymorphic liver enzyme which exhibits three phenotypes in the metabolism of CYP2C19 substrates; extensive metabolizers (*1/*1), intermediate metabolizers (*1/mutant) and poor metabolizers (mutant/mutant). Dexlansoprazole is the major circulating component in plasma regardless of CYP2C19 metabolizer status. In CYP2C19 intermediate and extensive metabolizers, the major plasma metabolites are 5-hydroxy dexlansoprazole and its glucuronide conjugate, while in CYP2C19 poor metabolizers dexlansoprazole sulfone is the major plasma metabolite.

Elimination

Following the administration of Dexilant, no unchanged dexlansoprazole is excreted in urine. Following the administration of [^{14}C] dexlansoprazole to 6 healthy male subjects, approximately 50.7% (standard deviation (SD): 9.0%) of the administered radioactivity was excreted in urine and 47.6% (SD: 7.3%) in the feces. Apparent clearance (CL/F) in healthy subjects was 11.4 to 11.6 L/h, respectively, after 5-days of 30 or 60 mg once daily administration.

Effect of CYP2C19 Polymorphism on Systemic Exposure of Dexlansoprazole

Systemic exposure of dexlansoprazole is generally higher in intermediate and poor metabolizers. In male Japanese subjects who received a single dose of Dexilant 30 mg or 60 mg (N=2 to 6 subjects/group), mean dexlansoprazole C_{max} and AUC values were up to 2 times higher in intermediate compared to extensive metabolizers; in poor metabolizers, mean C_{max} was up to 4 times higher and mean AUC was up to 12 times higher compared to extensive metabolizers. Though such study was not conducted in Caucasians and African Americans, it is expected dexlansoprazole exposure in these races will be affected by CYP2C19 phenotypes as well.

Effect of Food on Pharmacokinetics and Pharmacodynamics

In food-effect studies in healthy subjects receiving Dexilant under various fed conditions compared to fasting, increases in C_{max} ranged from 12% to 55%, increases in AUC ranged from 9% to 37%, and t_{max} varied (ranging from a decrease of 0.7 hours to an increase of 3 hours). No significant differences in mean intragastric pH were observed between fasted and various fed conditions. However, the percentage of time intragastric pH exceeded 4 over the 24-hour dosing interval decreased slightly when Dexilant was administered after a meal (57%) relative to fasting (64%), primarily due to a decreased response in intragastric pH during the first 4 hours after dosing. Because of this, while Dexilant can be taken without regard to food, some patients may benefit from administering the dose prior to a meal if post-meal symptoms do not resolve under post-fed conditions.

Special Populations

Pediatric Use

The pharmacokinetics of dexlansoprazole in patients under the age of 12 years have not been studied.

Patients 12 to 17 Years of Age

The pharmacokinetics of dexlansoprazole were studied in 36 patients with symptomatic GERD 12 to 17 years of age in a multi-center study. Patients were randomized to receive Dexilant 30 mg or 60 mg once daily for 7 days *(see Figure 2 and Table 3)*. In adolescents, dexlansoprazole mean Cmax was 81% to 105% of the adult mean C_{max} value, mean AUC was 78% to 88% of the adult mean AUC value, and mean CL/F was 112% to 132% of the adult mean CL/F value. Overall, dexlansoprazole

pharmacokinetics in patients 12 to 17 years of age were similar to those observed in healthy adults *(see Figure 1 and Table 2)*

Figure 2. Mean Dexlansoprazole Plasma Concentration – Time Profile Following Administration of 30 or 60 mg Dexlansoprazole Capsules Once Daily for 7 Days in Patients 12 to 17 Years of Age with Symptomatic GERD [33]

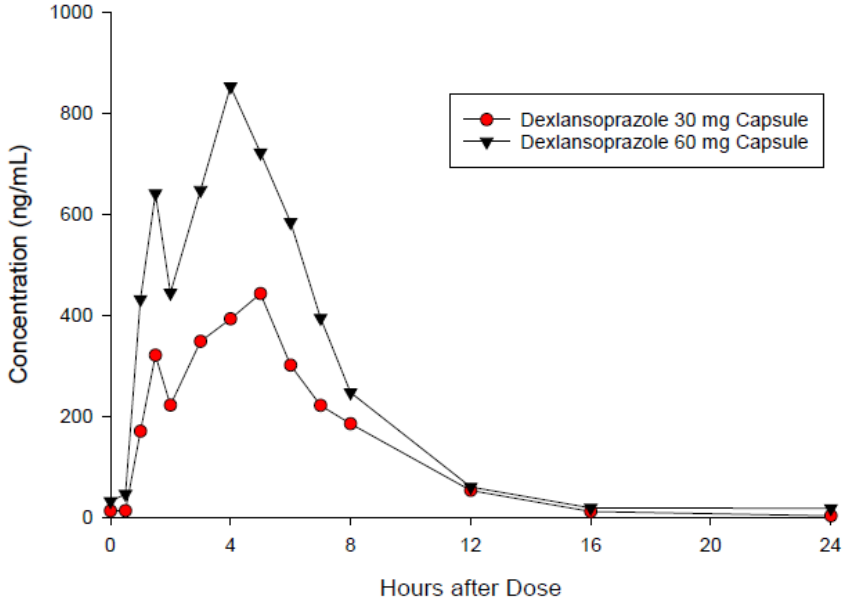


Table 3: Mean (CV%) Pharmacokinetic Parameters in Patients 12 to 17 Years of Age with Symptomatic GERD on Day 7 After Administration of Dexilant Once Daily for 7 Days			
Dose (mg)	**C_{max} (ng/ml)**	**AUC_{tau} (ng·h/mL)**	**CL/F (L/h)**
30 (N=17)	691 (53)	2886 (47)	12.8 (48)
60 (N=18)	1136 (51)	5120 (58)	15.3 (49)

Geriatric Use

The terminal elimination half-life of dexlansoprazole is significantly increased in geriatric subjects compared to younger subjects (2.23 and 1.5 hours, respectively); this difference is not clinically relevant. Dexlansoprazole exhibited higher systemic exposure (AUC) in geriatric subjects (34.5% higher) than younger subjects. No dosage adjustment is needed in geriatric patients *[see 8. RECOMMENDED DOSAGE].*

Renal Impairment

Dexlansoprazole is extensively metabolized in the liver to inactive metabolites, and no parent drug is recovered in the urine following an oral dose of dexlansoprazole. Therefore, the pharmacokinetics of dexlansoprazole are not expected to be altered in patients with renal impairment, and no studies were conducted in subjects with renal impairment *[see 8. RECOMMENDED DOSAGE]*. In addition, the pharmacokinetics of lansoprazole were studied in patients with mild, moderate or severe renal impairment; results demonstrated no need for a dose adjustment for this patient population.

Hepatic Impairment

In a study of 12 patients with moderately impaired hepatic function who received a single oral dose of Dexilant 60 mg, plasma exposure (AUC) of bound and unbound dexlansoprazole in the hepatic impairment group was approximately 2 times greater compared to subjects with normal hepatic function. This difference in exposure was not due to a difference in protein binding between the two liver function groups. No adjustment for Dexilant is necessary for patients with mild hepatic impairment (Child-Pugh Class A). Dexilant 30 mg should be considered for patients with moderate hepatic impairment (Child-Pugh Class B). No studies have been conducted in patients with severe hepatic impairment (Child-Pugh Class C) *[see 8. RECOMMENDED DOSAGE].*

Gender

In a study of 12 male and 12 female healthy subjects who received a single oral dose of Dexilant 60 mg, females had higher systemic exposure (AUC) (42.8% higher) than males. No dosage adjustment is necessary in patients based on gender.

Drug-Drug Interactions

Warfarin

In a study of 20 healthy subjects, co-administration of Dexilant 90 mg once daily for 11 days with a single 25 mg oral dose of warfarin on day 6 did not result in any significant differences in the pharmacokinetics of warfarin or INR compared to administration of warfarin with placebo. However, there have been reports of increased INR and prothrombin time in patients receiving PPIs and warfarin concomitantly *[see Interactions with other Medicaments (12.2)]*.

Cytochrome P 450 Interactions

Dexlansoprazole is metabolized, in part, by CYP2C19 and CYP3A4 *[see Pharmacokinetics Properties (4.3)]*.

In vitro studies have shown that dexlansoprazole is not likely to inhibit CYP isoforms 1A1, 1A2, 2A6, 2B6, 2C8, 2C9, 2D6, 2E1 or 3A4. As such, no clinically relevant interactions with drugs metabolized by these CYP enzymes would be expected. Furthermore, in vivo studies showed that Dexilant did not have an impact on the pharmacokinetics of coadministered phenytoin (CYP2C9 substrate) or theophylline (CYP1A2 substrate). The subjects' CYP1A2 genotypes in the drug-drug interaction study with theophylline were not determined. Although in vitro studies indicated that Dexilant has the potential to inhibit CYP2C19 in vivo, an in vivo drug-drug interaction study in mainly CYP2C19 extensive and intermediate metabolizers has shown that Dexilant does not affect the pharmacokinetics of diazepam (CYP2C19 substrate).

Clopidogrel

Clopidogrel is metabolized to its active metabolite in part by CYP2C19. A study of healthy subjects who were CYP2C19 extensive metabolizers, receiving once daily administration of clopidogrel 75 mg alone or concomitantly with Dexilant 60 mg (n=40), for 9 days was conducted. The mean AUC of the active metabolite of clopidogrel was reduced by approximately 9% (mean AUC ratio was 91%, with 90% CI of 86-97%) when Dexilant was coadministered compared to administration of clopidogrel alone. Pharmacodynamic parameters were also measured and demonstrated that the change in inhibition of platelet aggregation (induced by 5 mcM ADP) was related to the change in the exposure to clopidogrel active metabolite. The clinical significance of this finding is not clear.

5 NONCLINICAL TOXICOLOGY

5.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

The carcinogenic potential of dexlansoprazole was assessed using lansoprazole studies. In two 24-month carcinogenicity studies, Sprague-Dawley rats were treated orally with lansoprazole at doses of 5 to 150 mg per kg per day, about 1 to 40 times the exposure on a body surface (mg/m^2) basis of a 50 kg person of average height [1.46 m^2 body surface area (BSA)] given the recommended human dose of lansoprazole 30 mg per day.

Lansoprazole produced dose-related gastric ECL cell hyperplasia and ECL cell carcinoids in both male and female rats *[see Pharmacodynamics (4.2)].*

In rats, lansoprazole also increased the incidence of intestinal metaplasia of the gastric epithelium in both sexes. In male rats, lansoprazole produced a dose-related increase of testicular interstitial cell adenomas. The incidence of these adenomas in rats receiving doses of 15 to 150 mg per kg per day (4 to 40 times the recommended human lansoprazole dose based on BSA) exceeded the low background incidence (range = 1.4 to 10%) for this strain of rat.

In a 24-month carcinogenicity study, CD-1 mice were treated orally with lansoprazole doses of 15 to 600 mg per kg per day, 2 to 80 times the recommended human lansoprazole dose based on BSA. Lansoprazole produced a dose-related increased incidence of gastric ECL cell hyperplasia. It also produced an increased incidence of liver tumors (hepatocellular adenoma plus carcinoma). The tumor incidences in male mice treated with 300 and 600 mg lansoprazole per kg per day (40 to 80 times the recommended human lansoprazole dose based on BSA) and female mice treated with 150 to 600 mg lansoprazole per kg per day (20 to 80 times the recommended human lansoprazole dose based on

BSA) exceeded the ranges of background incidences in historical controls for this strain of mice. Lansoprazole treatment produced adenoma of rete testis in male mice receiving 75 to 600 mg per kg per day (10 to 80 times the recommended human lansoprazole dose based on BSA).
A 26-week p53 (+/-) transgenic mouse carcinogenicity study of lansoprazole was not positive.
Lansoprazole was positive in the Ames test and the *in vitro* human lymphocyte chromosomal aberration assay. Lansoprazole was not genotoxic in the *ex vivo* rat hepatocyte unscheduled DNA synthesis (UDS) test, the *in vivo* mouse micronucleus test or the rat bone marrow cell chromosomal aberration test.
Dexlansoprazole was positive in the Ames test and in the *in vitro* chromosome aberration test using Chinese hamster lung cells. Dexlansoprazole was negative in the *in vivo* mouse micronucleus test.
The potential effects of dexlansoprazole on fertility and reproductive performance were assessed using lansoprazole studies. Lansoprazole at oral doses up to 150 mg per kg per day (40 times the recommended human lansoprazole dose based on BSA) was found to have no effect on fertility and reproductive performance of male and female rats.

5.2 Animal Toxicology and/or Pharmacology

Reproductive Toxicology Studies

A reproduction study conducted in rabbits at oral dexlansoprazole doses up to 30 mg per kg per day (approximately 9 times the maximum recommended human dexlansoprazole dose [60 mg per day] based on BSA) revealed no evidence of impaired fertility or harm to the fetus due to dexlansoprazole. In addition, reproduction studies performed in pregnant rats with oral lansoprazole at doses up to 150 mg per kg per day (40 times the recommended human lansoprazole dose based on BSA) and in pregnant rabbits at oral lansoprazole doses up to 30 mg per kg per day (16 times the recommended human lansoprazole dose based on BSA) revealed no evidence of impaired fertility or harm to the fetus due to lansoprazole.

6 CLINICAL STUDIES

6.1 Healing of Erosive Esophagitis

Two multi-center, double-blind, active-controlled, randomized, 8-week studies were conducted in patients with endoscopically confirmed EE. Severity of the disease was classified based on the Los Angeles Classification Grading System (Grades A-D). Patients were randomized to one of the following three treatment groups: Dexilant 60 mg daily, Dexilant 90 mg daily or lansoprazole 30 mg daily. Patients who were *H. pylori* positive or who had Barrett's Esophagus and/or definite dysplastic changes at baseline were excluded from these studies. A total of 4092 patients were enrolled and ranged in age from 18 to 90 years (median age 48 years) with 54% male. Race was distributed as follows: 87% Caucasian, 5% Black and 8% other. Based on the Los Angeles Classification, 71% of patients had mild EE (Grades A and B) and 29% of patients had moderate to severe EE (Grades C and D) before treatment.
The studies were designed to test non-inferiority. If non-inferiority was demonstrated then superiority would be tested. Although non-inferiority was demonstrated in both studies, the finding of superiority in one study was not replicated in the other.
The proportion of patients with healed EE at week 4 or 8 is presented below in Table 4

Table 4: EE Healing Rates[a] in Adults: All Grades

Study	Number of Patients (N)[b]	Treatment Group (daily)	Week 4 % Healed	Week 8[c] % Healed	(95% CI) for the Treatment Difference (Dexilant–Lansoprazole) by Week 8
1	657	Dexilant 60 mg	70	87	(-1.5, 6.1)[d]
	648	Lansoprazole 30 mg	65	85	
2	639	Dexilant 60 mg	66	85	(2.2, 10.5)[d]
	656	Lansoprazole 30 mg	65	79	

CI = Confidence interval

[a] Based on crude rate estimates, patients who did not have endoscopically documented healed EE and prematurely discontinued were considered not healed.

[b] Patients with at least one post baseline endoscopy
[c] Primary efficacy endpoint
[d] Demonstrated non-inferiority to lansoprazole
Dexilant 90 mg was studied and did not provide additional clinical benefit over Dexilant 60 mg.

6.2 Maintenance of Healed Erosive Esophagitis

A multi-center, double-blind, placebo-controlled, randomized study was conducted in patients who successfully completed an EE study and showed endoscopically confirmed healed EE. Maintenance of healing and symptom resolution over a six-month period were evaluated with Dexilant 30 mg or 60 mg once daily compared to placebo. A total of 445 patients were enrolled and ranged in age from 18 to 85 years (median age 49 years), with 52% female. Race was distributed as follows: 90% Caucasian, 5% Black and 5% other.
Sixty-six percent of patients treated with 30 mg of Dexilant remained healed over the six-month time period as confirmed by endoscopy (see Table 5).

Table 5: Maintenance Rates[a] of Healed EE at Month 6 in Adults

Number of Patients (N)[b]	Treatment Group (daily)	Maintenance Rate (%)
125	DEXILANT 30 mg	66.4[c]
119	Placebo	14.3

[a] Based on crude rate estimates, patients who did not have endoscopically documented relapse and prematurely discontinued were considered to have relapsed
[b] Patients with at least one post baseline endoscopy
[c] Statistically significant vs placebo

Dexilant 60 mg was studied and did not provide additional clinical benefit over Dexilant 30 mg.
The effect of Dexilant 30 mg on maintenance of relief of heartburn was also evaluated. Upon entry into the maintenance study, a majority of patients' baseline heartburn severity was rated as none. Dexilant 30 mg demonstrated a statistically significantly higher percent of 24-hour heartburn-free periods compared to placebo over the 6-month treatment period (see Table 6). The majority of patients treated with placebo discontinued due to relapse of EE between month two and month six.

Table 6: Median Percentage of 24-Hour Heartburn-Free Periods of the Maintenance of Healed EE Study in Adults

	Overall Treatment[a]		Month 1		Month 6	
Treatment Group (daily)	N	Heartburn-Free 24-hour Periods (%)	N	Heartburn-Free 24-hour Periods (%)	N	Heartburn-Free 24-hour Periods (%)
Dexilant 30 mg	132	96.1[b]	126	96.7	80	98.3
Placebo	141	28.6	117	28.6	23	73.3

[a] Secondary efficacy endpoint
[b] Statistically significant vs placebo

6.3 Symptomatic Non-Erosive GERD

A multi-center, double-blind, placebo-controlled, randomized, 4-week study was conducted in patients with a diagnosis of symptomatic non-erosive GERD made primarily by presentation of symptoms. These patients who identified heartburn as their primary symptom, had a history of heartburn for 6 months or longer, had heartburn on at least 4 of 7 days immediately prior to randomization and had no esophageal erosions as confirmed by endoscopy. However, patients with symptoms which were not acid-related may not have been excluded using these inclusion criteria. Patients were randomized to one of the following treatment groups: Dexilant 30 mg daily, 60 mg daily, or placebo. A total of 947 patients were enrolled and ranged in age from 18 to 86 years (median age 48 years) with 71% female. Race was distributed as follows: 82% Caucasian, 14% Black and 4% other.

Dexilant 30 mg provided statistically significantly greater percent of days with heartburn-free 24-hour periods over placebo as assessed by daily diary over 4 weeks (see Table 7). Dexilant 60 mg was studied and provided no additional clinical benefit over Dexilant 30 mg.

Table 7: Median Percentages of 24-Hour Heartburn-Free Periods During the 4 Week Treatment Period of the Symptomatic Non-Erosive GERD Study in Adults

N	Treatment Group (daily)	Heartburn-Free 24-hour Periods (%)
312	Dexilant 30 mg	54.9[a]
310	Placebo	18.5

[a] Statistically significant vs placebo

A higher percentage of patients on Dexilant 30 mg had heartburn-free 24-hour periods compared to placebo as early as the first three days of treatment and this was sustained throughout the treatment period (percentage of patients on Day 3: Dexilant 38% versus placebo 15%; on Day 28: Dexilant 63% versus placebo 40%).

6.4 Pediatric GERD

Use of DEXILANT in patients 12 to 17 years of age is supported by evidence from adequate and well-controlled studies of DEXILANT capsules in adults, with additional safety, efficacy, and pharmacokinetic data from studies performed in pediatric patients.

Treatment of Symptomatic Non-Erosive GERD

In a single-arm, open-label, multi-center trial, 104 pediatric patients 12 to 17 years of age with symptomatic non-erosive GERD were treated with DEXILANT 30 mg capsules once daily, for four weeks to evaluate safety and effectiveness. Patients had a documented history of GERD symptoms for at least three months prior to screening, reported heartburn on at least three out of seven days during screening, and had no esophageal erosions as confirmed by endoscopy. The median age was 15 years, with females accounting for 70% of the patients. During the four week treatment period, the median percentage of 24 hour heartburn free periods was 47%.

Healing of EE, Maintenance of Healed EE and Relief of Heartburn: *Patients 12 to 17 Years of Age*

In a multi-center, 24-week study, 62 adolescents with a documented history of GERD for at least 3 months and endoscopically-proven EE were treated with dexlansoprazole 60 mg capsule once daily, for 8 weeks to evaluate safety and effectiveness. Patients ranged in age from 12 to 17 years (median age 15 years) with males accounting for 61% of the patients. Based on the Los Angeles Classification Grading Scale, 96.8% of the EE patients had mild EE (Grades A and B), and 3.2% of patients had moderate to severe EE (Grades C and D) before treatment.

EE healing rates in adolescents (87.9%) were similar to adults (85% - 87%) for up to 8 weeks of treatment.

After the initial 8 weeks of treatment, patients with endoscopically confirmed healed EE were randomized to receive treatment with dexlansoprazole 30 mg capsule or placebo, once daily for an additional 16 weeks. Eighty-two percent of patients treated with dexlansoprazole 30 mg capsule remained healed over the four-month treatment period as confirmed by endoscopy (*see Table 8*).

Table 8 Maintenance of Healed EE After 16 weeks in Patients 12 to 17 Years of Age

Number of Patients (N)	Treatment Group (Daily)	Maintenance Rate (%)
22	Dexlansoprazole 30 mg capsule	81.8
24	Placebo	58.3

During the 16 week maintenance period, median percentage of 24-hour heartburn-free periods were 86.6% for those receiving dexlansoprazole 30 mg capsule compared to 68.1% for those receiving placebo. The results for maintenance of healed EE and heartburn relief were similar to adults.

7. INDICATION

7.1 Healing of Erosive Esophagitis

DEXILANT is indicated in patients 12 years of age and older for healing of all grades of erosive esophagitis (EE) for up to 8 weeks.

7.2 Maintenance of Healed Erosive Esophagitis

DEXILANT is indicated for maintaining healing of erosive esophagitis and relief of heartburn for up to 4 months in adolescents 12 to 17 years of age and up to 6 months in adults.

7.3 Symptomatic Non-Erosive Gastroesophageal Reflux Disease

DEXILANT is indicated in patients 12 years of age and older for the treatment of heartburn associated with symptomatic non-erosive gastroesophageal reflux disease (GERD) for 4 weeks.

8. RECOMMENDED DOSAGE

DEXILANT is available as capsules in 30 mg and 60 mg strengths for adult use and patients 12 years of age and older. Directions for use in each indication are summarized in Table 9.

Table 9: DEXILANT Dosing Recommendations

Indication	Recommended Dose	Frequency
Healing of EE	60 mg	Once daily for up to 8 weeks
Maintenance of Healed EE and relief of heartburn	30 mg[a]	Once daily[b]
Symptomatic Non-Erosive GERD	30 mg	Once daily for 4 weeks

[a] In patients who had moderate or severe erosive esophagitis, a maintenance dose of 60mg may be used.

[b] Controlled studies did not extend beyond 6 months in adults, and beyond 4 months in adolescents 12 to 17 years of age.

No dosage adjustment for DEXILANT® is necessary for patients with mild hepatic impairment (Child-Pugh Class A). DEXILANT® 30 mg should be considered for patients with moderate hepatic impairment (Child-Pugh Class B). No studies have been conducted in patients with severe hepatic impairment (Child-Pugh Class C).

No dosage adjustment is necessary for elderly patients or for patients with renal impairment.

Patients should use the lowest dose and shortest duration of PPI therapy appropriate to the condition being treated.

Missed Dose

If a capsule is missed at its usual time, it should be taken as soon as possible. But if it is too close to the time of the next dose, only the prescribed dose should be taken at the appointed time. A double dose should not be taken.

9. MODE OF ADMINISTRATION

DEXILANT can be taken without regard to food.

DEXILANT should be swallowed whole.

DEXILANT should not be chewed.

For patients who have difficulty swallowing capsules, follow the instructions below for administration:

Administration with Water in an Oral Syringe

1. Open the capsule and empty the granules into a clean container with 20 mL of water.
2. Withdraw the entire mixture into a syringe.
3. Gently swirl the syringe in order to keep granules from settling.
4. Administer the mixture immediately into the mouth. Do not save the water and granule mixture for later use.
5. Refill the syringe with 10 mL of water, swirl gently, and administer.
6. Refill the syringe again with 10 mL of water, swirl gently, and administer.

Administration with Water via a Nasogastric Tube (≥ 16 French)

1. Open the capsule and empty the granules into a clean container with 20 mL of water.
2. Withdraw the entire mixture into a catheter-tip syringe.
3. Swirl the syringe gently in order to keep the granules from settling, and immediately inject the mixture through the nasogastric tube into the stomach. Do not save the water and granule mixture for later use.
4. Refill the syringe with 10 mL of water, swirl gently, and administer.
5. Refill the syringe again with 10 mL of water, swirl gently, and administer.

10. CONTRAINIDCATION

DEXILANT is contraindicated in patients with known hypersensitivity to any component of the formulation.

Hypersensitivity and anaphylaxis have been reported with DEXILANT use.

11. WARNINGS AND PRECAUTIONS

11.1 Gastric Malignancy

Symptomatic response with DEXILANT does not preclude the presence of gastric malignancy.

11.2 *Clostridium Difficile* Associated Diarrhea

Published observational studies suggest that PPI therapy like DEXILANT may be associated with an increased risk of *Clostridium difficile* associated diarrhea, especially in hospitalized patients. This diagnosis should be considered for diarrhea that does not improve. [see *Adverse Effects/ Undesirable Effects (14.2 Post Marketing Experience)].*

Patients should use the lowest dose and shortest duration of PPI therapy appropriate to the condition being treated.

11.3 Bone Fracture

Proton pump inhibitors, especially if used in high doses and over long durations (>1 year), may modestly increase the risk of hip, wrist and spine fracture, predominantly in the elderly or in presence of other recognised risk factors. Observational studies suggest that proton pump inhibitors may increase the overall risk of fracture by 10-40%. Some of this increase may be due to other risk factors. Patients at risk of osteoporosis should receive care according to current clinical guidelines and they should have an adequate intake of vitamin D and calcium.

11.4 Influence on Vitamin B-12 Absorption

Daily treatment with any acid-suppressing medications over a prolonged period of time (e.g. longer than 3 years) may lead to malabsorption of cyanocobalamin (vitamin B-12) caused by hypo- or achlorhydria. Rare reports of cyanocobalamin deficiency occurring with acid-suppressing therapy have been reported in the literature. This diagnosis should be considered if clinical symptoms consistent with cyanocobalamin deficiency are observed.

11.5 Interference with Laboratory Tests

Increased Chromogranin A (CgA) level may interfere with investigations for neuroendocrine tumors. If the patient(s) are due to have a test on Chromogranin A level, Dexilant treatment should be stopped for at least 5 days before CgA measurements to avoid this interference (see section Pharmacodynamic). If CgA and gastrin levels have not returned to reference range after initial measurement, measurements should be repeated 14 days after cessation of proton pump inhibitor treatment.

11.6 Hypomagnesemia

Severe hypomagnesaemia has been rarely reported in patients treated with PPIs like Dexilant for at least three months, and in most cases for a year, Serious manifestations of hypomagnesaemia such as fatigue, delirium, convulsions, dizziness and ventricular arrhythmia can occur but they may begin insidiously and be overlooked. Hypomagnesemia may lead to hypocalcemia and/ or hypokalemia (see section *Adverse Effects*). In most affected patients, hypomagnesaemia (and hypomagnesaemia

associated hypocalcemia and/or hypokalemia) improved after magnesium replacement and discontinuation of the PPI.

For patients expected to be on prolonged treatment or who take PPI with digoxin or drugs that may cause hypomagnesaemia (e.g., diuretics), health care professionals should consider measuring magnesium levels before starting PPI treatment and periodically during treatment.

11.7 Concomitant use of DEXILANT with Methotrexate
Literature suggests that concomitant use of PPIs with methotrexate (primarily at high dose; see methotrexate prescribing information) may elevate and prolong serum levels of methotrexate and/or its metabolite, possibly leading to methotrexate toxicities. In high-dose methotrexate administration, a temporary withdrawal of the PPI may be considered in some patients.

11.8 Regular Surveillance
Patients on proton pump inhibitor treatment (particularly those treated for long term) should be kept under regular surveillance.

11.9 Severe Cutaneous Adverse Reactions
Severe cutaneous adverse reactions, including Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), drug reaction with eosinophilia and systemic symptoms (DRESS), acute generalized exanthematous pustulosis (AGEP) and erythema multiforme have been reported in association with the use of PPIs (see section Adverse Effects). Discontinue dexlansoprazole at the first signs or symptoms of severe cutaneous adverse reactions or other signs of hypersensitivity and consider further evaluation.

11.10 Subacute Cutaneous Lupus Erythematosus (SCLE)
Proton pump inhibitors are associated in rare cases with the occurrence of subacute cutaneous lupus erythematosus (SCLE). If lesions occur, especially in sun exposed areas of the skin, and if accompanied by arthralgia, the patient should seek medical help promptly and the healthcare professional should consider stopping Dexilant. SCLE after previous treatment with a proton pump inhibitor may increase the risk of SCLE with other proton pump inhibitors.

12. INTERACTIONS WITH OTHER MEDICAMENTS

12.1 Drugs with pH-Dependent Absorption Pharmacokinetics
DEXILANT causes inhibition of gastric acid secretion. DEXILANT is likely to substantially decrease the systemic concentrations of the HIV protease inhibitors, such as atazanavir and nelfinavir, which are dependent upon the presence of gastric acid for absorption, and may result in a loss of therapeutic effect of atazanavir or nelfinavir and the development of HIV resistance. Therefore, DEXILANT should not be co-administered with atazanavir or nelfinavir.
DEXILANT may interfere with the absorption of other drugs where gastric pH is an important determinant of oral bioavailability (e.g., ampicillin esters, digoxin, iron salts, ketoconazole).

12.2 Warfarin
Co-administration of DEXILANT 90 mg and warfarin 25 mg did not affect the pharmacokinetics of warfarin or INR. However, there have been reports of increased INR and prothrombin time in patients receiving PPIs and warfarin concomitantly. Increases in INR and prothrombin time may lead to abnormal bleeding and even death. Patients treated with DEXILANT and warfarin concomitantly may need to be monitored for increases in INR and prothrombin time.

12.3 Tacrolimus
Concomitant administration of dexlansoprazole and tacrolimus may increase whole blood levels of tacrolimus, especially in transplant patients who are intermediate or poor metabolizers of CYP2C19.

12.4 Clopidogrel
Concomitant administration of dexlansoprazole and clopidogrel in healthy subjects had no clinically important effect on exposure to the active metabolite of clopidogrel or clopidogrel-induced platelet

inhibition. No dose adjustment of clopidogrel is necessary when administered with an approved dose of DEXILANT.

12.5 Methotrexate

Case reports, published population pharmacokinetic studies, and retrospective analyses suggest that concomitant administration of PPIs and methotrexate (primarily at high dose; see methotrexate prescribing information) may elevate and prolong serum levels of methotrexate and/or its metabolite hydroxymethotrexate. However, no formal drug interaction studies of high-dose methotrexate with PPIs have been conducted.

13. STATEMENT ON USAGE DURING PREGNANCY AND LACTATION

Pregnancy

Teratogenic Effects

Pregnancy Category B. There are no adequate and well-controlled studies with dexlansoprazole in pregnant women. There were no adverse fetal effects in animal reproduction studies of dexlansoprazole in rabbits. Because animal reproduction studies are not always predictive of human response, DEXILANT should be used during pregnancy only if clearly needed.

A reproduction study conducted in rabbits at oral dexlansoprazole doses up to approximately 9 times the maximum recommended human dexlansoprazole dose (60 mg per day) revealed no evidence of impaired fertility or harm to the fetus due to dexlansoprazole. In addition, reproduction studies performed in pregnant rats with oral lansoprazole at doses up to 40 times the recommended human lansoprazole dose and in pregnant rabbits at oral lansoprazole doses up to 16 times the recommended human lansoprazole dose revealed no evidence of impaired fertility or harm to the fetus due to lansoprazole.

Nursing Mothers

It is not known whether dexlansoprazole is excreted in human milk. However, lansoprazole and its metabolites are present in rat milk following the administration of lansoprazole. As many drugs are excreted in human milk, and because of the potential for tumorigenicity shown for lansoprazole in rat carcinogenicity studies, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

14. ADVERSE EFFECTS/UNDESIRABLE EFFECTS

14.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

The safety of DEXILANT was evaluated in 4548 patients in controlled and uncontrolled clinical studies, including 863 patients treated for at least 6 months and 203 patients treated for one year. Patients ranged in age from 18 to 90 years (median age 48 years), with 54% female, 85% Caucasian, 8% Black, 4% Asian, and 3% other races. Six randomized controlled clinical trials were conducted for the treatment of EE, maintenance of healed EE, and symptomatic GERD, which included 896 patients on placebo, 455 patients on DEXILANT 30 mg, 2218 patients on DEXILANT 60 mg, and 1363 patients on lansoprazole 30 mg once daily.

Most Commonly Reported Adverse Reactions

The most common adverse reactions (≥2%) that occurred at a higher incidence for DEXILANT than placebo in the controlled studies are presented in Table 10.

Table 10: Incidence of Adverse Reactions in Controlled Studies

Adverse Reaction	Placebo (N=896) %	DEXILANT 30 mg (N=455) %	DEXILANT 60 mg (N=2218) %	DEXILANT Total (N=2621) %	Lansoprazole 30 mg (N=1363) %
Diarrhea	2.9	5.1	4.7	4.8	3.2
Abdominal Pain	3.5	3.5	4.0	4.0	2.6
Nausea	2.6	3.3	2.8	2.9	1.8
Upper Respiratory Tract Infection	0.8	2.9	1.7	1.9	0.8
Vomiting	0.8	2.2	1.4	1.6	1.1

Flatulence	0.6	2.6	1.4	1.6	1.2

Adverse Reactions Resulting in Discontinuation

In controlled clinical studies, the most common adverse reaction leading to discontinuation from DEXILANT therapy was diarrhea (0.7%).

Other Adverse Reactions

Other adverse reactions that were reported in controlled studies at an incidence of less than 2% are listed below by body system:

Blood and Lymphatic System Disorders: anemia, lymphadenopathy

Cardiac Disorders: angina, arrhythmia, bradycardia, chest pain, edema, myocardial infarction, palpitation, tachycardia

Ear and Labyrinth Disorders: ear pain, tinnitus, vertigo

Endocrine Disorders: goiter

Eye Disorders: eye irritation, eye swelling

Gastrointestinal Disorders: abdominal discomfort, abdominal tenderness, abnormal feces, anal discomfort, Barrett's esophagus, bezoar, bowel sounds abnormal, breath odor, colitis microscopic, colonic polyp, constipation, dry mouth, duodenitis, dyspepsia, dysphagia, enteritis, eructation, esophagitis, Fundic Gland Polyps (Benign), gastritis, gastroenteritis, gastrointestinal disorders, gastrointestinal hypermotility disorders, GERD, GI ulcers and perforation, hematemesis, hematochezia, hemorrhoids, impaired gastric emptying, irritable bowel syndrome, mucus stools, oral mucosal blistering, painful defecation, proctitis, paresthesia oral, rectal hemorrhage, retching

General Disorders and Administration Site Conditions: adverse drug reaction, asthenia, chest pain, chills, feeling abnormal, inflammation, mucosal inflammation, nodule, pain, pyrexia

Hepatobiliary Disorders: biliary colic, cholelithiasis, hepatomegaly

Immune System Disorders: hypersensitivity

Infections and Infestations: candida infections, influenza, nasopharyngitis, oral herpes, pharyngitis, sinusitis, viral infection, vulvo-vaginal infection

Injury, Poisoning and Procedural Complications: falls, fractures, joint sprains, overdose, procedural pain, sunburn

Laboratory Investigations: ALP increased, ALT increased, AST increased, bilirubin decreased/increased, blood creatinine increased, blood gastrin increased, blood glucose increased, blood potassium increased, liver function test abnormal, platelet count decreased, total protein increased, weight increase

Metabolism and Nutrition Disorders: appetite changes, hypercalcemia, hypokalemia

Musculoskeletal and Connective Tissue Disorders: arthralgia, arthritis, muscle cramps, musculoskeletal pain, myalgia

Nervous System Disorders: altered taste, convulsion, dizziness, headaches, migraine, memory impairment, paresthesia, psychomotor hyperactivity, tremor, trigeminal neuralgia

Psychiatric Disorders: abnormal dreams, anxiety, depression, insomnia, libido changes

Renal and Urinary Disorders: dysuria, micturition urgency

Reproductive System and Breast Disorders: dysmenorrhea, dyspareunia, menorrhagia, menstrual disorder

Respiratory, Thoracic and Mediastinal Disorders: aspiration, asthma, bronchitis, cough, dyspnoea, hiccups, hyperventilation, respiratory tract congestion, sore throat

Skin and Subcutaneous Tissue Disorders: acne, dermatitis, erythema, pruritis, rash, skin lesion, urticaria

Vascular Disorders: deep vein thrombosis, hot flush, hypertension

Additional adverse reactions that were reported in a long-term uncontrolled study and were considered related to DEXILANT by the treating physician included: anaphylaxis, auditory hallucination, B-cell lymphoma, bursitis, central obesity, cholecystitis acute, dehydration, diabetes mellitus, dysphonia, epistaxis, folliculitis, gout, herpes zoster, hyperlipidemia, hypothyroidism, increased neutrophils, MCHC decrease, neutropenia, rectal tenesmus, restless legs syndrome, somnolence, tonsillitis.
Other adverse reactions not observed with DEXILANT, but occurring with the racemate lansoprazole can be found in the lansoprazole prescribing information, ADVERSE REACTIONS section.

Pediatrics

The safety of DEXILANT capsules were evaluated in controlled and single-arm clinical trials including 104 pediatric patients,12 to 17 years of age for the relief of heartburn *[see Clinical Studies*

6.4)].
The adverse reaction profile was similar to that of adults. The most common adverse reactions that occurred in ≥5% of patients were diarrhea, headache and abdominal pain,

14.2 Post-marketing Experience

The following adverse reactions have been identified during post-approval of DEXILANT. As these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.
Blood and Lymphatic System Disorders: autoimmune hemolytic anemia, idiopathic thrombocytopenic purpura
Ear and Labyrinth Disorders: deafness
Eye Disorders: blurred vision
Gastrointestinal Disorders: oral edema, pancreatitis, microscopic colitis
General Disorders and Administration Site Conditions: facial edema
Hepatobiliary Disorders: drug-induced hepatitis
Immune System Disorders: anaphylactic shock (requiring emergency intervention), exfoliative dermatitis, Infections and Infestations: *Clostridium difficile* associated diarrhea
Metabolism and Nutrition Disorders: hypomagnesemia, hyponatremia, vitamin B12 deficiency, hypocalcemia≠, hypokalemia≠
Musculoskeletal System Disorders: fracture of the hip, wrist or spine
Nervous System Disorders: cerebrovascular accident, transient ischemic attack
Renal and Urinary Disorders: acute renal failure, Tubulointerstitial nephritis (TIN) (with possible progression to renal failure)
Respiratory, Thoracic and Mediastinal Disorders: pharyngeal edema, throat tightness
Skin and Subcutaneous Tissue Disorders: generalized rash, leucocytoclastic vasculitis, Stevens-Johnson Syndrome, Toxic Epidermal Necrolysis (some fatal), subacute cutaneous lupus erythematosus, Drug reaction with eosinophilia and systemic symptoms, Acute generalized exanthematous pustulosis, Erythema multiforme
≠ hypocalcemia and/ or hypokalemia may be related to the occurrence of hypomagnesemia (see *Special Warnings and Special Precautions for Use*)

15. OVERDOSE AND TREATMENT

The effects of overdose of dexlansoprazole in humans are not known (although the acute toxicity is likely to be low) and, consequently, instruction for treatment cannot be given.

There have been no reports of significant overdose of Dexilant. Multiple doses of Dexilant 120 mg and a single dose of Dexilant 300 mg did not result in death or other severe adverse events. Serious adverse reactions of hypertension have been reported in association with twice daily doses of Dexilant 60 mg. Non serious adverse reactions observed with twice daily doses of Dexilant 60 mg include hot flushes, contusion, oropharyngeal pain, and weight loss.

In the case of suspected overdose the patient should be monitored. Dexlansoprazole is not significantly eliminated by haemodialysis. If necessary, gastric emptying, charcoal and symptomatic therapy is recommended.

16. STORAGE CONDITIONS

Store below 30°C.
Shelf life
3 years.

17. DOSAGE FORMS AND PACKAGING AVAILABLE

Packs of 7 and 14 capsules.
Not all pack sizes may be marketed.

18. NAME AND ADDRESS OF MANUFACTURER/MARKETING AUTHORIZATION HOLDER

Manufacturer

Takeda GmbH
Lehnitzstrasse 70-98, 16515 Oranienburg, Germany

Product Registration Holder
Takeda Malaysia Sdn Bhd
Unit TB-L13-1, Level 13, Tower B, Plaza 33,
No. 1, Jalan Kemajuan, Seksyen 13
46200 Petaling Jaya, Selangor, Malaysia

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